(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 November 2004 (18.11.2004)

PCT

(10) International Publication Number
WO 2004/099140 A1

(51) International Patent Classification[7]: C07D 209/14

(21) International Application Number: PCT/IN2003/000180

(22) International Filing Date: 8 May 2003 (08.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **HETERO DRUGS LIMITED** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500 018, Andhrapradesh (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PARTHASARADHI REDDY, Bandi** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500 018, Andhrapradesh (IN). **RATHNAKAR REDDY, Kura** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN). **RAJI REDDY, Rapolu** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN). **MURALIDHARA REDDY, Dasari** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN). **SUBASH CHANDER REDDY, Kesireddy** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

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(54) Title: NOVEL CRYSTALLINE FORMS OF SUMATRIPTAN SUCCINATE

(57) Abstract: The present invention relates to novel crystalline forms of sumatriptan succinate, to processes for their preparation and to pharmaceutical compositions containing them.

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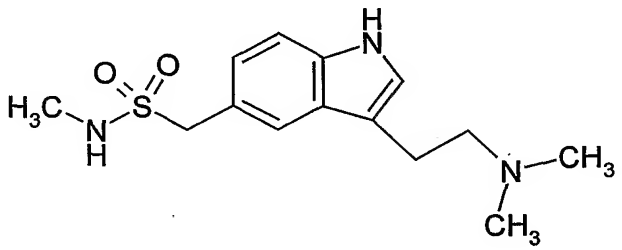
NOVEL CRYSTALLINE FORMS OF SUMATRIPTAN SUCCINATE

FIELD OF THE INVENTION

The present invention relates to novel crystalline forms of sumatriptan succinate, to processes for their preparation and to pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Sumatriptan succinate is a selective 5-Hydroxy tryptamine$_1$ receptor subtype agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide succinate (1:1). Sumatriptan succinate is currently used in the treatment of migraine. Sumatriptan is represented by the following structure:



Sumatriptan and related compounds, processes for their preparation and their therapeutic uses were disclosed in US 4,816,470.

Processes described in the literature do not produce well-defined, consistently reproducible crystalline forms of sumatriptan succinate. So, there is a need for stable, consistently reproducible crystalline forms of sumatriptan succinate for handling and for better pharmaceutical compositions.

It has now been discovered that sumatriptan succinate can be prepared in two well-defined, stable and consistently reproducible crystalline forms.

The object of the present invention is to provide stable, consistently reproducible crystalline forms of sumatriptan succinate, processes for preparing these forms and pharmaceutical compositions comprising them.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of sumatriptan succinate. This crystalline form is designated as sumatriptan succinate form I and typical form I x-ray powder diffraction spectrum of sumatriptan succinate form I is shown in figure 1.

Sumatriptan succinate form I is characterized by peaks in the powder x-ray diffraction spectrum having two-theta angle positions at about 9.3, 12.4, 12.8, 13.4, 15.6, 15.8, 16.3, 16.5, 18.2, 19.0, 20.0, 20.4, 20.7, 21.5, 22.2, 22.9, 26.1, 27.1, 28.7 and 29.8 degrees.

In accordance with the present invention, a process is provided for preparation of sumatriptan succinate form I. Sumatriptan succinate form I is prepared by dissolving sumatriptan free base in a suitable solvent, adding succinic acid to the solution and then isolating sumatriptan succinate form I from the solution.

Sumatriptan free base may be dissolved in a sufficient volume of the suitable solvent at elevated temperature (up to reflux). The amount of succinic acid is not critical, but 0.5 – 2.0 moles per mole of sumatriptan free base is preferable.

The 'suitable solvents' are selected from acetone, diethyl ketone, methyl ethyl ketone, methyl isobutyl ketone, methyl propyl ketone, methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butyl alcohol, tetrahydrofuran, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl acetate, ethyl formate, methyl formate, diethyl ether, diisopropyl ether and tert-butyl methyl ether. A mixture of these solvents may also be used. Preferable solvents are acetone, methanol, ethanol, tetrahydrofuran, tert-butyl methyl ether and ethyl acetate.

In accordance with the present invention, there is provided a novel crystalline form of sumatriptan succinate. This crystalline form is designated as sumatriptan succinate form II and typical form II x-ray powder diffraction spectrum of sumatriptan succinate form II is shown in figure 2.

Sumatriptan succinate form II is characterized by peaks in the powder x-ray diffraction spectrum having two-theta angle positions at about 6.2, 7.7, 13.9, 15.1, 17.5, 17.9, 19.1, 19.4, 20.3, 20.8, 21.5, 22.4, 23.2, 23.9, 26.4 and 31.8 degrees.

In accordance with the present invention, a process is provided for preparation of sumatriptan succinate form II. Sumatriptan succinate form II is prepared by dissolving sumatriptan free base in a chlorinated solvent, adding succinic acid to the solution and then isolating sumatriptan succinate form II from the solution.

Sumatriptan free base may be dissolved in a sufficient volume of the chlorinated solvent at elevated temperature (up to reflux). The amount of succinic acid is not critical, but 0.5 – 2.0 moles per mole of sumatriptan free base is preferable.

The chlorinated solvents are selected from methylene dichloride, chloroform, carbon tetrachloride and ethylene dichloride. A mixture of these solvents may also be used. Preferable solvents are chloroform and methylene dichloride.

Sumatriptan obtained by a previously known method may be used in the above processes.

In accordance with the present invention, there is provided a pharmaceutical composition comprising sumatriptan succinate form I and a pharmaceutically acceptable carrier or diluent.

In accordance with the present invention, there is provided a pharmaceutical composition comprising sumatriptan succinate form II and a pharmaceutically acceptable carrier or diluent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction spectrum of sumatriptan succinate form I.

Figure 2 is a x-ray powder diffraction spectrum of sumatriptan succinate form II.

x-Ray powder diffraction spectrum was measured on a Bruker axs D8 advance x-ray powder diffractometer having a copper-Kα radiation.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

Example 1

Sumatriptan free base (5.0 gm) is added to acetone (50 ml), the contents are heated to reflux to form a clear solution and then succinic acid (2.0 gm) is added to the solution. The contents are stirred for 2 hours at reflux temperature, allowed to cool to 25^{0}C and filtered to give 5.6 gm of sumatriptan succinate form I.

Example 2

Sumatriptan free base (10.0 gm) is mixed with methanol (120 ml), heated to reflux to form a clear solution and then succinic acid (4.0 gm) is added to the solution. The contents are stirred for 5 hours at reflux temperature, cooled slowly to 25^{0}C and filtered to give 10.8 gm of sumatriptan succinate form I.

Example 3

Sumatriptan free base (5.0 gm) is mixed with chloroform (50 ml), the contents are heated to reflux to form a clear solution and then succinic acid (2 gm) is added to the solution. The reaction mixture is stirred for 3 hours at reflux temperature, allowed to cool to 25^{0}C and filtered to give 5.1 gm of sumatriptan succinate form II.

Example 4

Sumatriptan free base (10.0 gm) is mixed with methylene dichloride (150 ml), the contents are heated to reflux and then succinic acid (4.0 gm) is added to the clear solution formed. The contents are stirred for 4 hours at reflux temperature, cooled slowly to 25^{0}C and filtered to give 10.5 gm of sumatriptan succinate form II.

We claim:

1. A crystalline sumatriptan succinate form I, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 9.3, 12.4, 12.8, 13.4, 15.6, 15.8, 16.3, 16.5, 18.2, 19.0, 20.0, 20.4, 20.7, 21.5, 22.2, 22.9, 26.1, 27.1, 28.7 and 29.8 degrees.
2. A crystalline sumatriptan succinate form I as defined in claim 1, further characterized by an x-ray powder diffraction spectrum as in figure 1.
3. A process for preparation of sumatriptan succinate form I as defined in claim 1, which comprises the steps of:

a) dissolving sumatriptan free base in a suitable solvent;
b) adding succinic acid; and
c) isolating sumatriptan succinate form I;

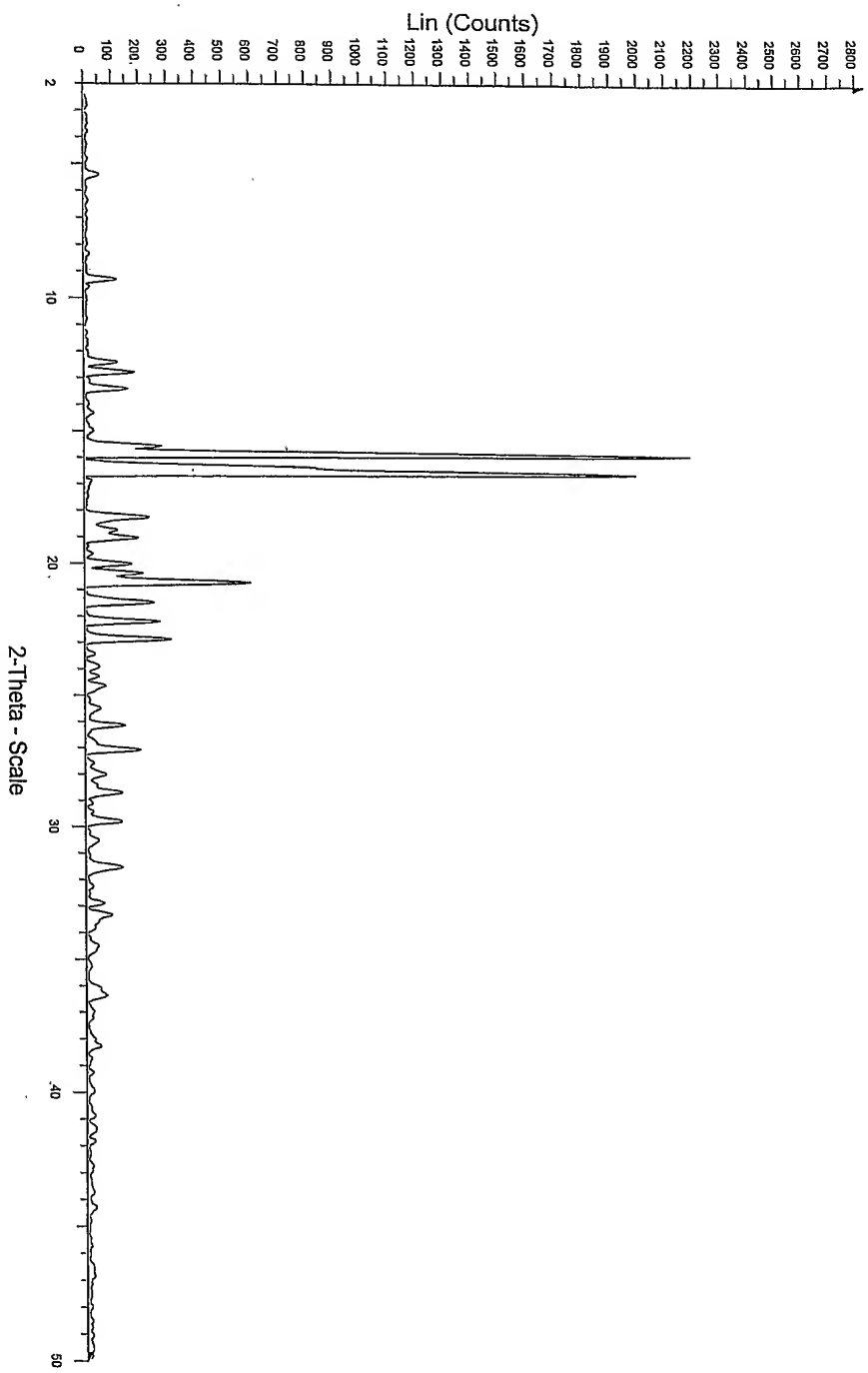
wherein the suitable solvent is selected from acetone, diethyl ketone, methyl ethyl ketone, methyl isobutyl ketone, methyl propyl ketone, methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butyl alcohol, tetrahydrofuran, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl acetate, ethyl formate, methyl formate, diethyl ether, diisopropyl ether and tert-butyl methyl ether.

4. A process according to claim 3, wherein the suitable solvent is selected from acetone, methanol, ethanol, tetrahydrofuran, tert-butyl methyl ether and ethyl acetate.
5. A process according to claim 3 or 4, wherein the suitable solvent is methanol.
6. A crystalline sumatriptan succinate form II, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at 6.2, 7.7, 13.9, 15.1, 17.5, 17.9, 19.1, 19.4, 20.3, 20.8, 21.5, 22.4, 23.2, 23.9, 26.4 and 31.8 degrees.
7. A crystalline sumatriptan succinate form II as defined in claim 6, further characterized by an x-ray powder diffraction spectrum as in figure 2.
8. A process for preparation of sumatriptan succinate form II as defined in claim 6, which comprises the steps of:

a) dissolving sumatriptan free base in a chlorinated solvent;
b) adding succinic acid; and
c) isolating sumatriptan succinate form II;

wherein the chlorinated solvent is selected from the group consisting of methylene dichloride, chloroform, carbon tetrachloride and ethylene dichloride.

9. A process according to claim 8, wherein the chlorinated solvent is chloroform.
10. A process according to claim 8, wherein the chlorinated solvent is methylene dichloride.
11. A pharmaceutical composition comprising sumatriptan succinate form I of claim 1 and a pharmaceutically acceptable carrier or diluent.
12. A pharmaceutical composition comprising sumatriptan succinate form II of claim 6 and a pharmaceutically acceptable carrier or diluent.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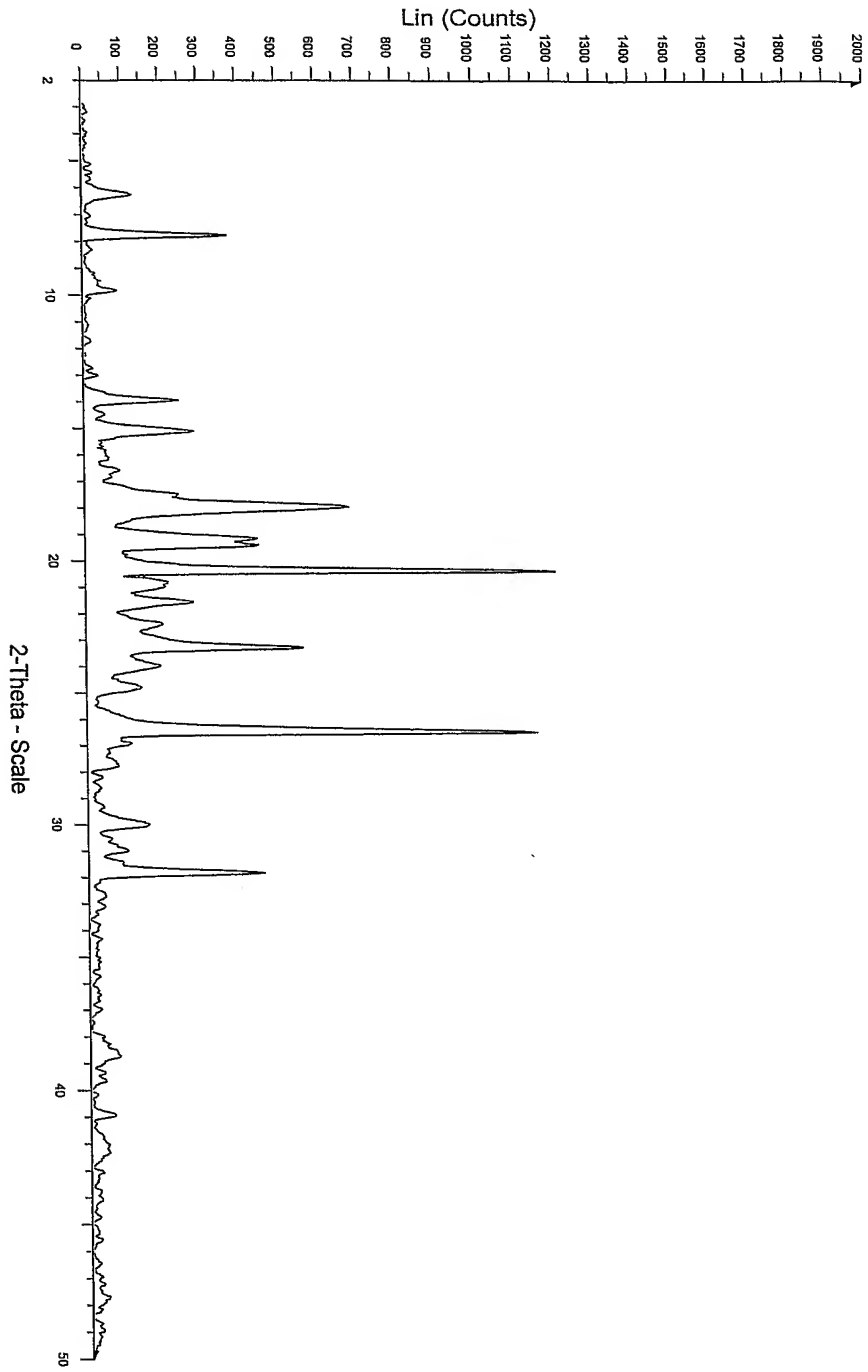
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00180-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 209/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D 209/14

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPOQUE: WPI, EPODOC, STN (Karlsruhe) CAS: REGISTRY and CA databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2162522 A (GLAXO GROUP LIMITED) 6 February 1986 (06.02.86) *example 9, example 18.*	1-12
A	ES 2033578 A1 (INKE S. A.) 16 March 1993 (16.03.93) *example 3.*	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 January 2004 (15.01.2004)	12 February 2004 (12.02.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer SLABY S. Telephone No. 1/53424/348

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte...ional application No.
PCT/IN 03/00180-0

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